

“Because new grounds of rejection are raised herein, this action is not final.” The Examiner confirmed by telephone that the Action is Non-Final.

Rejections under 35 U.S.C. §103:

Claims 1-5, 10-16, 22, 23 and 26-44 are newly rejected under 35 U.S.C. §103(a) as obvious over Del Tito et al. in view of Nakamura et al., Zhang et al., Saier, Sprinzl et al., Kawakami et al., and Clouthier et al. The Office Action states that “Del Tito et al. teach the construction and use of a plasmid, pRI952, which comprises an array of two tRNA genes (argU and IleX) encoding tRNAs specific for the rarely used codons AGG/AGA and AUA, respectively.” The Office Action states that “Del Tito et al. do not explicitly teach the use of a vector comprising an array of two or three or more tRNAs corresponding to rarely used codons for overexpression of a heterologous gene comprising rarely used codons of any species other than E. coli.” The Office Action concludes, however, that it would have been obvious at the time of the invention to modify the vector construct taught by Del Tito et al. for compensating for the presence of rarely used codons present in the gene encoding a protein of interest by interchanging and/or adding different tRNA genes corresponding to other rarely used codons in a given cell type, because Del Tito et al. teach that it is within the skill of the art to carefully scrutinize the coding sequence of a protein, identify rarely used codons and compensate for the presence of such rare codons by supplying in trans the tRNA corresponding to the identified rarely used codons from a vector expressing different tRNA genes, and because the rarely used codons and corresponding genes were widely known in the art (i.e., the teachings of Nakamura et al., Zhang et al., Saier, Sprinzl et al., Kawakami et al. and Clouthier et al.). Applicants respectfully disagree.

Claims 1-5, 10-16, 22, 23 and 26-38 are rejected under 35 U.S.C. §103(a) as obvious over Del Tito et al. in view of Makoff et al. This rejection was maintained from the previous Action. Claims 6-9, 19, 21, 24 and 25 are rejected under 35 U.S.C. §103(a) as obvious over Del Tito et al. in view of Makoff et al. as applied above and further in view of the 1997 Novagen catalog (pages 42-44). This rejection was maintained from the previous Action. Claims 18 and 20 are rejected under 35 U.S.C. §103(a) as obvious over Del Tito et al. in view of Makoff et al. and the 1997 Novagen catalog as applied above and further in view of Wnendt. This rejection

was maintained from the previous Action. Claims 39-44 are rejected under 35 U.S.C. §103(a) as obvious over Del Tito et al.

Applicant respectfully disagrees with each of the above grounds of rejection on the basis that the commercial success of the claimed invention provides an objective indication of non-obviousness sufficient to overcome the rejections.

The Examiner has discounted Applicant's previous showing of commercial success as an objective indicator of non-obviousness. The Office Action states:

"the evidence of record does not indicate that the level of commercial sales of a couple of specific embodiments of the claimed invention is necessarily due to some aspect of the claimed invention. Without the appropriate background against which to judge (e.g., a commercially available vector comprising the tRNA genes taught by Del Tito et al.) it is impossible to make the judgment that there is some aspect of applicants' invention that contributes to significant commercial success or that the demonstrated sales are of such a magnitude as to make the claimed invention unobvious over the prior art."

Applicant submits that commercial success is an established indicator of nonobviousness and must be taken into account in considering the issue of obviousness. That evidence of such success is "secondary" in time does not mean that it is secondary in importance. Evidence of secondary considerations may often be the most probative and cogent evidence in the record. *Trustwall Systems Corp. v. Hydro-Air Engineering Inc.*, 813 F.2d 1207, 2 U.S.P.Q.2d 1034 (Fed. Cir. 1987). A showing of commercial success of a claimed invention, *whenever such success occurs*, is relevant in resolving the issue of nonobviousness. *Lindemann Maschinenfabrik GmbH v. American hoist & Derrick Co.*, 730 F.2d 1452, 1461, 221 U.S.P.Q. 481, 487 (Fed. Cir. 1984); emphasis added.

Applicant submits that the law does not impose a standard that there must be a product on the market embodying the exact prior art before commercial sales figures can be considered an indicator of non-obviousness. Such a standard imposes a burden on the applicant that could not be met even in the face of astronomical sales, if no commercial product exactly embodying the prior art is available. Applicant submits that, to the contrary, the absence of a commercial embodiment of the prior art composition would, if anything, support the non-obviousness of a claimed product for which there are significant sales. That is, it is reasonable to look upon the

absence of a commercial product embodying Del Tito's construct (which has two tRNA genes (argU and ileX)), not to mention the absence of a product embodying a construct that comprises an array of three or more tRNA genes as claimed, as simply further indicative that the claimed invention is non-obvious.

Second, Applicant submits that while there are no sales figures for the exact construct taught by Del Tito et al., the sales figures reported in the two prior Rule 132 Declarations of Mary Buchanan report the sales of host cells comprising recombinant genes encoding two rare-codon tRNAs. Specifically, in addition to reporting the sales figures for an embodiment of competent cells comprising three recombinant rare-codon tRNAs (BL21-CodonPlus™ RIL and BL21-CodonPlus™ (DE3) RIL Competent Cells; the "RIL products"), the Rule 132 Declaration of Mary Buchanan filed February 9, 2001 also reports the sales of BL21-CodonPlus™ RP Competent Cells and BL21-CodonPlus™ (DE3) RP Competent Cells (the "RP products"), each of which has two recombinant rare-codon tRNA genes (argU and proL). The following table, assembled from the sales figures in the Buchanan declaration, shows that the RIL products outsold the RP products by *greater than 2-fold, or by greater than 100%*. The data for 1999 and 2000 only are compared because the data for 2001 represent only a small fraction of the year (only through February 8).

A. Compare sales of RIL products to sales of RP products:

Year	RIL products (3 tRNAs)	RP products (2 tRNAs)
1999	\$428,625	\$64,816
2000	\$290,763	\$198,757
Total 1999 + 2000	\$719,388	\$263,573
Ratio:	2.73	
Total RIL/ Total RP		

Applicant submits that a greater than 100% difference (2.73-fold) in sales of RIL host cells (which comprise a recombinant DNA molecule which comprises an array of three tRNA genes that correspond to codons that are rarely used in the host cell), relative to the sales of RP host cells (which comprise only two rare-codon tRNAs), is sufficient to demonstrate the non-obviousness of the claimed host cells that comprise an array of three or more rare-codon tRNA genes. Applicant wishes to emphasize that the sale price of the RIL products and the RP products was the same, \$195/ml, as stated in Mary Buchanan's Declaration. Therefore, the sales figures directly reflect the relative units of each product sold, permitting an accurate comparison without need for adjustment for differences in sale price. That is, more than twice as many, and in fact, *almost three times as many* units of the host cells comprising an array of three rare-codon tRNAs were sold than host cells comprising only two rare-codon tRNAs. Given that the difference in sales was not by a mere few percentage points, but by well over 100%, Applicants submit that the differences in sales are sufficient to demonstrate the non-obviousness of the claimed invention.

Applicant notes that the Office Action refers to "the commercial success of a few specific embodiments" in discounting the importance of the commercial success. However, applicable case law states that one need not show that all possible elements within the claims were successfully commercialized in order to rely upon the success of the embodiment commercialized to overcome alleged obviousness. *Applied Materials Inc. v. Advanced Semiconductor Materials*, 40 U.S.P.Q.2d 1481, 1486 (Fed. Cir. 1996)

In a similar vein, the Office Action states that "there is no evidence of record that whatever commercial success seen for embodiments that function in *E. coli* would necessarily be observed for embodiments that are intended for use in other cell types (e.g., maize, *B. subtilis*, *S. aureus*, *D. melanogaster*, etc.)." Applicant submits that "[a] showing of commercial success of a claimed invention, *whenever such success occurs*, is relevant in resolving the issue of nonobviousness." *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1461 (Fed. Cir. 1984); emphasis added. Thus, the question is not whether commercial success would *necessarily* be realized for other embodiments, but whether the commercial success of the embodiments commercialized is sufficient to demonstrate nonobviousness. Applicant submits that total sales of more than \$740,000 for host cells

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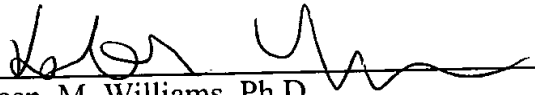
comprising an array of three tRNA genes that correspond to codons that are rarely used in the host cell, over the period reported in the Declaration of Mary Buchanan, are more than sufficient to demonstrate non-obviousness, particularly when considering that host cells comprising only two recombinant rare-codon tRNA genes were outsold by more than 2 to 1.

In view of the above, Applicant submits that claims 1-16 and 18-44 are not obvious over the combination of references cited.

Applicant submits that in view of the preceding remarks, all issues raised in the Office Action have been addressed herein. Applicants respectfully request reconsideration of the claims.

Respectfully submitted,

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Kathleen M. Williams, Ph.D.
Registration No. 34,380
Customer No.: 27495
PALMER & DODGE LLP
111 Huntington Avenue
Telephone: (617) 239-0451
Telecopier: (617) 227-4420